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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,311	08/23/2006	Francisco Javier Vila Pahi	Q108487	8146

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EXAMINER	
KRISHNAN, GANAPATHY	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,311	VILA PAHI ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12,14-17,19-23,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-12,14-17,19-23,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 2/26/2009 has been entered.

The Request for Continued Examination filed 2/26/2009 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 2, 13, 18 and 24-25 have been canceled.

2. New Claims 26-27 have been added.

3. Claims 1, 3-5, 9-10, 14, 16, 19 and 23 have been amended.

4. Remarks drawn to rejections under 35 USC 112, first and second paragraphs and 103.

Claims 1, 3-12, 14-17, 19-23 and 26-27 are pending in the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of osteoarthritis, does not reasonably

provide enablement for the prophylaxis of osteoarthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of predictability in the art
(D) The amount of direction provided by the inventor
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claims 26-27 are drawn to a method of prophylaxis of osteoarthritis via administration to a mammal in need thereof an effective amount of inulin polysulfate in acid form or as a physiologically acceptable salt thereof. Applicants have not provided a definition for the term prophylaxis. The ordinary dictionary meaning (AskOxford.com) of the term prophylaxis is prevention or protective treatment of a disease. The scope of the claims is seen to include the administration of the said compounds to a healthy mammal, and subsequent exposure to conditions that would cause osteoarthritis, wherein the said compounds prevents said exposure from manifesting itself in said mammal so exposed.

The state of the prior art

The examiner notes that the art used in the rejections below and WO 03/006645 cited by the applicants teach treatment of osteoarthritis, rheumatoid arthritis and other antiinflammatory conditions. According to The Merck Manual (16^{th} Edition, 1992, pages 1338-42) teaches that etiology is unknown and appears to be a complex set of interactions. The pathophysiologic process proceeds to the appearance of symptoms and signs, varying degrees of disability with no predictability, arrest or even reversal. Treatment includes rehabilitation to prevent dysfunction or disability and its severity. Drugs like aspirin and corticosteroids are useful for treatment.

The level of predictability in the art

Based on the teaching of the prior art above there is not seen sufficient data to substantiate the prevention of osteoarthritis using a sulfated polysaccharide as instantly claimed. Based on the teaching of the prior art the prevention of osteoarthritis is highly unpredictable.

The amount of direction provided by the inventor

Even though the instant specification provides a reference to laminarin sulfate as a heparanase inhibitor and its association with arthritis it is still not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the prevention of osteoarthritis using a single active agent as instantly claimed.

The existence of working examples

The working examples set forth in the instant specification are drawn to the effect of inulin polysulfate on the synthesis of aggrecans. One of ordinary skill in the art will not extrapolate the results of the instant examples to the prevention of osteoarthritis using the active agent as instantly claimed.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

In view of the information set forth, the instant disclosure is not seen to be sufficient to enable the prevention or prophylaxis of osteoarthritis as instantly claimed. One of ordinary skill in the art would have to perform additional experimentation with different sulfated polysaccharides using healthy mammals, with regard to variables the dosage and frequency, etc. inorder to determine the preventive efficacy of the instant active agents.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 recites the terms, 'whose structure is derived from a sulfated polysaccharide' followed by Markush members. It is not clear what applicants intend. If applicants intend derivatives of the recited sulfated polysaccharides, in the absence of the specific derivatizations to the chemical core claimed or distinct language to describe the

structural modifications or the chemical names of the derivatives of this invention, the identity of said derivatives would be difficult to define and the metes and bounds of the said derivatives applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claim(s). The recitation of how the sulfated oligosaccharide is produced is not given patentable weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-12, 14-17, 19-23 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cullis-Hill et al (US 5,145,841) in view of Komai et al (International Journal of Biological Macromolecules, 2002, 30, 197-204), Dictionary.com (2002, page 3) all of record and Martindale: The Extra Pharmacopoeia 1996, page 11 (cited by applicants).

Hill et al, drawn to antiinflammatory compounds, teach that polysulfated polysaccharides like alginic acid, pectin and inulin have a variety of biological activities including antiinflammatory activity (col. 5, lines 53-64) and are useful for treatment of osteoarthritis (col. 7, lines 39-40; col. 8, lines 46-59; col. 12, lines 8-26; col. 24, lines 37-39). According to Hill the sodium salt of polysulfated xyloside is an inhibitor of PMN elastase and other enzymes that degrade connective tissue and articular cartilage. The polysulfated xyloside binds to articular cartilage and connective tissues (col. 6, lines 32-46) and promotes joint hyaluronate and articular cartilage which provide the rheological properties (col. 7, lines 14-24). The said sulfated polysaccharides can also be used as their salts (col. 9, lines 55-58). Hill discloses that the polysulfated polysaccharides abbreviated as SP 54 and Arteparon that are inhibitors of cartilage degrading enzymes had a sulfur content (i.e., degree of sulfation) of about 16% and 13% respectively (col. 6, lines 8-11 and 57-61) and also discloses that selectivity of biological activity of the polysulfated polysaccharides is desirable and has been achieved by varying the degree of sulfate substitution (col. 7, lines 51-54). Even though the degree of sulfation taught by

Hill is lower that that claimed in instant claims 9-10 and his reference to degree of sulfation may be in the context of anticoagulant activity, it is a suggestion to one of ordinary skill in the art to adjust the degree of sulfation (as one of the variables) inorder to achieve optimal beneficial effects.

Komai et al teach the use of gellan sulfate (one of the sulfated polysaccharide instantly claimed) for providing therapeutic benefits to patients with rheumatoid arthritis (abstract; page 198, first full paragraph and figure 2). However, Komai et al do not specifically teach or exemplify the use of gellan sulfate for the treatment of osteoarthritis.

According to definitions in Dictionary.com both rheumatoid and osteoarthritis involve degradation of bone joints. According to Martindale both osteoarthritis and rheumatoid arthritis are characterized by degradation/destruction of cartilage.

According to Hill polysulfated xyloside binds to articular cartilage and connective tissues (col. 6, lines 32-46) and promotes joint hyaluronate and articular cartilage which provide the rheological properties. This means that gellan sulfate would also be expected to bind to the articular cartilage and connective tissues and perform the same function.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the polysulfated polysaccharides as instantly claimed in a method of treating osteoarthritis since the use of the sulfated polysaccharides as instantly claimed is seen to be suggested for the treatment of the related rheumatoid arthritis. Both osteoarthritis and rheumatoid arthritis are characterized by degradation/destruction of cartilage.

One of skill in the art would be motivated to use the active agents in the method of treatment as instantly claimed since they inhibit the release and action of the serine

proteinases. The proteoglycans, which confer the property of resilience of the joints, are depleted due to excessive degradation of proteinases. Hence inhibition of the degradation of the proteinases inhibits the depletion of the proteoglycans, which are needed to maintain the resilience of joints. One of skill in the art would expect structurally related polysulfate polysaccharides to perform the same functions and would look for other related sulfated polysulfated polysaccharides and oligosaccharides for use in the method of treatments as instantly claimed.

Response to Applicants Arguments

Applicants have traversed the rejection under 35 USC 103 of record arguing that:

1. The office action has ignored the well-established differences between osteoarthritis and rheumatoid arthritis. Osteoarthritis is a degenerative joint disease and rheumatoid arthritis is an inflammatory disease which involves an immunological component. Even though there may be synovial inflammation observed with advanced osteoarthritis it is well recognized in the art that such inflammation is different in nature to that observed with rheumatoid arthritis.

2. Hill discloses the use of metallic complexes of polysulfated polysaccharides. The metal alters the conformation and the rigidity of the polymer chain thereby influencing its biological activity. This is a teaching away from the instant invention.

3. Neither Hill nor Komai teach or suggest oral administration.

Applicants' arguments have been considered but are not found to be persuasive.

Rheumatoid arthritis may have an immunological component. But according to the prior art both joint and cartilage degradation/destruction take place in rheumatoid

arthritis and osteoarthritis and sulfated polysaccharides inhibit enzymes that are responsible for such degradation. Applicants have just argued that synovial inflammation observed with advanced osteoarthritis it is different in nature to that observed with rheumatoid arthritis but have not shown how it is different and why the same treatment of both will not work. Reference to Martindale's article regarding this aspect of the disease is not seen sufficient.

The reference to Hill's teaching that metal in their complex alters the conformation and the rigidity of the polymer (polysaccharide) chain thereby influencing its biological activity is not seen as a teaching away from the instant invention. Hill does not specifically teach that the presence of the metal destroys its biological activity. The term influencing will not be interpreted by one of ordinary skill in the art as teaching away from the instant invention especially when Hill teaches that such complexes are useful for treating both osteoarthritis and rheumatoid arthritis and also shows such treatments using animal models. Moreover, the use of salts and of active agents and oral administration of active agents in treatment methods is well known to one of ordinary skill in the art. Such need not be specifically taught by the art. The instant invention is seen to be rendered obvious by the prior art.

Conclusion

Claims 1, 3-12, 14-17, 19-23 and 26-27 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
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